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10/501,412	07/12/2004	Amedeo De Tomassi	ITR0037YP	6096

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MERCK AND CO., INC
P O BOX 2000
RAHWAY, NJ 07065-0907

EXAMINER	
POPA, ILEANA	
ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,412	DE TOMASSI ET AL.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20,24 and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *20* is/are allowed.

6)☒ Claim(s) *1-6,8-19,24 and 27* is/are rejected.

7)☒ Claim(s) *7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office action.

Election/Restrictions

2. It is noted that a restriction requirement was mailed on 01/09/2007. Upon further consideration, the restriction requirement is withdrawn. Accordingly, claims 6 are and 15-19 are hereby rejoined.

3. Claims 21-23, 25, 26, and 28-47 have been cancelled. Claims 1, 3, 8, and 27 have been amended.

Claims 1-20, 24, and 27 are under pending and under examination.

Response to Arguments

Claim Rejections - 35 USC § 112, 2nd paragraph

4. The rejection of claims 24 and 27 rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, is withdrawn. Applicant's arguments filed 08/03/2007 have been fully considered and are persuasive.

Applicant traversed the instant rejection on the grounds that one of skill in the art would understand what the claims refer to when reciting the term "curing the cell" and that the specification teaches a number of ways to cure a cell (p. 19, lines 3-6). Applicant submits that he does not believe that reciting the steps of one particular

method of curing a cell is essential to the claim. Applicant points out that the specification describes the characteristics of a cured cell as a cell that formerly contained a replicating replicon and does not currently contain that replicon or detectable levels of replicon RNA (p. 31, lines 6-8). Therefore, Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged and, while curing the cell is essential for the methods recited in claims 24 and 27 and the claims should recite the steps leading to the cured cell, the claims will be interpreted to encompass providing a nucleic acid of a GBV-B replicon, and any step that materially results in a GBV-B containing cell.

5. The rejection of claim 13 under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements is withdrawn in response to Applicant's arguments filed on 08/03/2007.

Claim Rejections - 35 USC § 112, enablement

6. Claims 24 and 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is withdrawn in response to Applicant's amendments to the claims, filed on 08/03/2007.

Claim Rejections - 35 USC § 103

7. The rejection of claims 1, 2, 12, and 13 under 35 U.S.C. 103(a) as being unpatentable over either Lohmann et al. (Science, 1999, 285: 110-113) or Blight et al. (Science, 2000, 290: 1972-1974), in view of each Lanford et al. (J Virol, 2001, 75: 8074-8081), Khromykh et al. (J Virol, 1997, 71: 1497-1505) and Hong et al. (PGPUB 2001/0034019) is maintained for the reasons of record forth in the non-final Office action. Applicant's arguments filed 08/03/2007 have been fully considered but they are not persuasive.

Applicant traversed the instant rejection on the grounds that (i) Lanford et al. state that an HCV replicon system " cannot replace the need for a virus-based culture system and small animal model" (p. 8074, column 2, lines 17-20), and therefore, this disclosure would not motivate one of skill in the art to make a GBV replicon, (ii) Hong et al. disclose chimeric full length viruses with a GBV genome that has been modified by replacing a non-structural gene with the analogous gene from HCV (paragraph 0029, lines 1-8); Applicant argues that Hong et al. do not disclose replicons or a virus containing GBV non-structural genes, since at least one of the genes in the constructs of Hong et al. is an HCV equivalent (paragraph 0057), and (iii) there is no motivation or suggestion to apply the teachings of replicons of Lohmann et al., Blight et al., or Khromykh et al. to GBV or to combine Lohmann et al., Blight et al., or Khromykh et al. with the teachings of full length viruses of Lanford et al. or Hong et al. Additionally,

Applicant argues that the Examiner used hindsight in applying the instant rejection. Therefore, Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged, however, the rejection is maintained for the following reasons:

In response to applicant's argument that the Examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

With respect to Lanford et al., it is noted that their teachings only pertain to HCV and not GBV. Applicant's argument that Lanford et al. teach that HCV replicons cannot replace the need of virus-based culture system and small animal models is taken out of context. Lanford et al. only teach that, even if HCV replicons are useful, they cannot compensate for the advantages offered by GBV, i.e., robust replication *in vitro* and ability to infect small animals as opposed to low replicative capacity and ability to only infect very large animals (p. 8074, column 2, first full paragraph). Lanford et al. do teach that the use of GBV overcomes the limitations of HCV (p. 8074, column 2, p. 8080, column 1, first paragraph). Nowhere in their paper do they teach that GBV replicons would not be desirable, on the contrary, Lanford et al. do teach that replicons

are useful to advance HCV studies. Therefore, based on these teachings, one of skill in the art would realize that the advantage of using a GBV replicon would be high replication rates and the use of small an inexpensive animal models. Moreover, Khromykh et al. teach that replicons, wherein large regions of structural proteins are deleted, offer the major advantage of isolating viral replication from virion assembly and maturation, and therefore, are useful for the identification RNA sequences and proteins directly involved in viral replication (p. 1497, column 1). Therefore, Applicant's argument that, by reading Lanford et al., one of skill in the art would not be motivated to construct a GBV replicon is not found persuasive. With respect to Hong et al., it is noted that the reference was not cited for teaching replicons; the reference was only cited to evidence that, by applying the teachings of either Lohmann et al. or Blight et al. taken with Khromykh et al., one of skill in the art would have necessarily obtained a subgenomic GBV-B replicon comprising the 5' of GBV-B consisting of nucleotides 1-445 of SEQ ID NO: 1), the 3'-UTR of GBV-B consisting of nucleotides 7710-8069 of SEQ ID NO: 1, and an NS3-NS5b sequence consisting of nucleotides 1938-7709 of SEQ ID NO: 1, as recited in claim 1 (see the non-final Office action).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re*

Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, both Lohmann et al. and Blight et al. teach a subgenomic HCV replicon (see the non-final Office action). Although neither Lohmann et al. nor Blight et al. teach a subgenomic GBV-B replicon, the prior art teaches the advantage of obtaining similar subgenomic replicons with deletions in the genomic region encoding structural proteins for a variety of positive strand viruses (see the teachings of Khromykh et al. as disclosed in the non-final Office action). In addition to Khromykh et al., Lanford et al. teach HCV replicons and the necessity of using these replicons to advance HCV studies (p. 8074, column 2, first full paragraph). Since Lanford et al. teach that GBV is a better system (see above and the non-final Office action), one of skill in the art would have been motivated to obtain GBV replicons. Since the art teaches that HCV replicons can be successfully obtained and that GBV is the closest relative of HCV based on sequence homology, genome organization, and liver tropism, one of skill in the art would have been expected to have a reasonable expectation of success in obtaining such GBV replicons. Therefore, the combination of references above renders the claimed invention *prima facie* obvious.

New Rejections

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made

to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-6, 8-19, 24, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lohmann et al., in view of each Lanford et al., Khromykh et al., Hong et al., and De Francesco et al. (WO 02/059321).

Lohmann et al. teach a subgenomic HCV replicon comprising in order: the HCV 5'-UTR, a HCV structural region (i.e., the structural region is functionally coupled to the 5' UTR), a neomycin phosphodiesterase gene (*neo*) as a selection sequence, the ECMV internal ribosome entry site (IRES), a NS3-NS5B sequence functionally coupled to the EMCV IRES and an AUG initiation codon, and an HCV 3'-UTR, wherein the HCV replicon is capable of replication in Huh-7 cells (claims 1, 2, and 14), wherein the replicon is part of an expression vector comprising a promoter functionally coupled to the replicon nucleotide sequence (claim 12), and wherein the expression vector comprising the replicon is used in a process of making the replicon, wherein the process of making comprises transfecting cells with the expression vector and isolating the replicon (claim 13) (see Lohmann et al., Abstract, p. 110, columns 2 and 3, p. 111, columns 1 and 2, Fig 1, p. 112, column 3, p. 113, column 2). Lohmann et al. do not teach a subgenomic GBV-B replicon (claims 1, 2, 12, and 13). However, it would have been obvious tone of skill in the art, at the time the invention was made, to obtain a subgenomic GBV replicon by to applying the teachings of Lohmann et al., with a reasonable expectation of success. The motivation to do obtain a subgenomic replicon is provided by Khromykh et al., who teach that replicons whith large regions of structural

proteins deleted offer the major advantage of isolating viral replication from virion assembly and maturation, and therefore, are useful for the identification RNA sequences and proteins directly involved in viral replication (p. 1497, column 1). The motivation to apply the teachings of Lohmann et al. to GBV-B is provided by Lanford et al., who teach that GBV-B is better suited to be used in HCV antiviral studies because it replicates it replicates *in vitro* at levels that are 1,000-10,000 fold higher than the ones of HCV and because it can be used in small and inexpensive animals (Abstract, p. 8074, column 2, p. 8075, column 1, first full paragraph, p. 8080, column 1). One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that HCV replicons can be successfully obtained and that GBV is the closest relative of HCV based on sequence homology, genome organization, and liver tropism.

It is noted that, by applying the above teachings, one of skill in the art would have necessarily obtained a subgenomic GBV-B replicon comprising the 5' and 3'-UTR of GBV-B (i.e., nucleotides 1-445 and 7710-8069 of SEQ ID NO: 1, respectively), a GBV structural region, *neo* gene as a selection sequence, encephalomyocarditis virus IRES (nucleotides 1324-1934 of SEQ ID NO: 1), NS3-NS5b (nucleotides 1935-7709 of SEQ ID NO: 1 or nucleotides 2642-3265 of SEQ ID NO: 2), or an NS2-NS5b, wherein NS2 consists of the nucleotides 2643-3265 of SEQ ID NO: 2 (claims 1-5 and 8-10) (compare Fig. 1 of Lohmann et al. with Fig.4 of the instant application; see Hong et al., p. 1, paragraphs 0002 and 0010, and sequence alignment, of record). It is noted that, with the exception of encephalomyocarditis virus IRES and the *neo* gene, the sequences

above are the GBV equivalents of the HCV sequences used by Lohmann et al. to construct their replicon; the encephalomyocarditis virus IRES and the *neo* gene were well known in the art before the invention was made and were used by Lohmann et al. to obtain the HCV replicon. It is also noted that the structural region of Lohmann et al. consists of the first 12-16 amino acids (i.e., the first 36-48 nucleotide) of the core protein (p. 113, column 2); therefore, one of skill in the art would have known to include the first 36 to 48 nucleotide of the HCV core protein (i.e., nucleotides 446-511, 446-487, 446-469 of SEQ ID NO: 1) (claims 3-5). In addition to the above, Lohmann et al. teach that the structural region could comprise the first 30-48 nucleotide of the HCV core protein and the E1 protein, i.e., nucleotides 446-2641 of SEQ ID NO: 2 (see Fig. 1 A) (claims 6 and 8-10). Therefore, by exactly applying the teachings of Lohmann et al., one of skill in the art would have achieved the claimed invention.

Lohmann et al., taken with Lanford et al., Khromykh et al., Hong et al. do not teach a method of making a second replicon from a first replicon (claims 1 and 16), nor do they teach a method of measuring the ability of a compound to affect GBV-B replicon activity (calims 18 and 19) or a method of making a GBV-B replicon enhanced cell, wherein the enhanced cell further comprises a functional GBV-B replicon (claims 24 and 27). De Francesco et al. teach the following: (i) making a second HCV replicon by transfecting Huh7 cells with a first HCV replicon, isolating the replicon, and sequencing the replicon (claims 15 and 16); (ii) measuring the ability of a compound to affect HCV replicon activity by providing the compound a Huh7 cell comprising the replicon and measuring the ability of the compound to affect replicon activity (claims 17-19); (iii)

making a HCV replicon enhanced cell by introducing and maintaining a first HCV replicon into the cell, curing the cell of the replicon, and introducing and maintaining a second HCV replicon into the cell (claims 24 and 27) (p. 3, lines 11-15, p. 4, lines 1-10 and 14-35, p. 5, lines 1 and 2, claims 24-26, 28-31, and 34). It would have been obvious to one of skill in the art, at the time the invention was made, to use the replicon of Lohmann et al. or Blight et al. taken with Lanford et al., Khromykh et al., and Hong et al., in the methods of De Francesco et al., with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to obtain replicons with enhanced replicative capacity, to test compounds for antiviral activity, and to obtain cells capable of sustaining enhanced viral replication. One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that such cells can be successfully obtained.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

10. Claims 1-6, 8-19, 24, and 27 are rejected.

Claim 7 is objected to foe being dependent from the rejected claim 1.

Claims 7 and 20 are free of prior art because the art does not specifically teach SEQ ID NO: 1.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD

/Joseph Woitach/

Joseph Woitach

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